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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/306,986	05/07/1999	THUAN QUOC TRINH	0942.4570001	4261

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/306,986	TRINH ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13 and 56-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13 and 56-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 12/19/2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/306,986 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants request to enter the previously unentered amendment filed on October 19, 2001 in the prior nonprovisional application is acknowledged and this amendment has been entered.

2. Applicants cancellation of claims 38-55 without prejudice, amendment of claim 8, and addition of claims 56-69, Paper No. 13, 10/19/2001, is acknowledged. Claims 8-13 and 56-69 are at issue and are present for examination.

Applicants' arguments filed on 12/19/2001, Paper No. 16, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

3. Acknowledgment is made of applicant's claim of the benefit of Provisional Application No: 60/084,737. It is noted, however, that applicant has not made such a statement on the first line of the specification. An application in which the benefits of an

earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Applicants filing of information disclosures, Paper No. 4, filed 9/1/1999, and Paper No. 5, filed 9/23/1999, is acknowledged. Those references considered have been initialed. Copies of the initialed 1449's were supplied in a prior office action Office action, Paper No. 9, 1/02/2001.

Drawings

5. The drawings are objected to for the reasons stated on the Notice of Draftpersons Patent Drawing Review (PTO-948).

Correction is required.

Specification

6. The disclosure is objected to because of the following informalities:

As discussed above under "Priority", an application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

On page 20, lines 3-7, the specification recites "...from crude preparations of DNA from any cell or tissue such as viral, bacteriophage, bacteria, insect, bird, fish plant, yeast,...". The inclusion of "viral" and "bacteriophage" in the group of cells or tissues is objected to because viruses and bacteriophages are not cells or tissues.

Appropriate correction is required.

Claim Objections

7. Claim 8 is objected to because of the following informalities: Claim 8 a) recites "mixing the crude preparation containing DNA wherein the DNA functions...". It is suggested that the placement of a comma after "containing DNA" such as "mixing the crude preparation containing DNA_1 wherein the DNA functions...", would make the recitation easier to read. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 8-13 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 8 (9-13 and 56 dependent on) is indefinite in that it is unclear and vague in the recitation "a crude preparation containing DNA" because it is unclear what is to be encompassed by "a crude preparation containing DNA". While " preparation containing DNA" appears to be well defined as its literal interpretation, one of skill in the art would not necessarily know how the term "crude" is to be defined and thus this makes a "crude preparation containing DNA" somewhat unclear and therefore the claim is indefinite.

Applicants traverse this rejection on the basis that the term "crude preparation" is described in the specification as a preparation that contains some nucleic acids that have been released from cells without the need for purification of the nucleic acid from the cells. Applicants point to the specification page 20, lines 7-12 as supporting their argument:

> Preparation of crude extracts of cells or tissues may be accomplished by standard procedures which allow removal of at least some nucleic acids from cells or tissue without the need for purification of the nucleic acids from the cells, tissue or cell/tissue debri, although nucleic acids may be isolated or purified or partially purified prior to the use in accordance with the invention.

This argument is not found persuasive as applicants response to the previous rejection as well as the referred to passage in the specification do not clearly define what is meant by a "crude preparation containing DNA". Applicants further ask that explanation be given as to why the term "crude preparation" is indefinite. In response to applicants traversal, as stated previously, no guidance is given as to the metes and bounds of what is considered to be a "crude preparation containing DNA" thus the claim remains unclear and therefore indefinite. Furthermore applicants response suggests that they intended "crude preparation containing DNA" to be limited to cell extracts

which would exclude for example "mini-preped DNA". The vast majority of skilled artisans in the field of molecular biology would consider "mini-preped DNA" to be a "crude preparation" yet applicants appear to intend to exclude this from the scope of the term. As such the metes and bounds of the term is unclear.

Further support of the indefiniteness of the term "crude preparation" can be seen in the differing interpretations of this term by the applicants and the examiner with respect to the previous art rejections. For the purpose of advancing prosecution, absent a definition to the contrary, a crude preparation containing DNA is interpreted by the office as any preparation containing DNA along with other cellular material (i.e. RNA, proteins etc...).

If applicants intend "crude preparation containing DNA" to be limited to an unpurified cell/tissue extract containing DNA as the response appears to suggest, it is suggested that the claims be amended to recite unpurified cell lysate.

10. Claim 56 is indefinite in the recition "...wherein said crude preparation containing DNA is from any cell or tissue selected from the group consisting of virus; bacteriophage; bacteria; insect; bird; fish; plant; yeast;...". The inclusion of "virus" and "bacteriophage" in the group of cells or tissues is indefinite in that it is confusing because viruses and bacteriophages are not cells or tissues.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

11. Claims 8-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Maudru et al. (Journal of Virological Methods 66: 247-261, July 1997).

The rejection was originally stated as it applies to claims 8-12 in an earlier office action.

Maudru et al. examine the cause of and teach a method for the elimination of background signals in a modified polymerase chain reaction-based reverse transcriptase assay. Maudru et al. teach that the background signal of the PCR-based reverse transcriptase (PBRT) assay was due to an intrinsic RNA-dependent DNA polymerase activity of the *Taq* DNA polymerase enzyme used for the assay. They further teach that this background signal could be eliminated by inserting a ribonuclease digestion step prior to amplifying/synthesizing the cDNA product of the RT reaction by PCR. Thus Maudru et al. teach a method for synthesizing a nucleic acid molecule from a crude preparation containing DNA, said method comprising mixing the crude preparation containing DNA, wherein the DNA functions as a desired nucleic acid

template, with one or more DNA polymerases (*Taq* DNA Polymerase), and one or more peptides or polypeptides having ribonuclease activity (Boehringer-Mannheim Catalog No: 119-915, "heterogeneous mixture of ribonucleases"), a suitable buffer, and nucleotides and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template. It is acknowledged that Maudru et al. teach a method of nucleic acid synthesis that begins with a RNA-containing preparation, but this is converted to a DNA-containing preparation during the reverse transcriptase step. It is at this point where Maudru et al. anticipates the claimed methods in that the starting material is now a DNA containing preparation and in as much as no additional purification steps have been done to this preparation and the preparation clearly comprises at least DNA, RNA and proteins, it could be considered a "crude preparation containing DNA" (See above 112 2nd paragraph rejection).

Thus Maudru et al. anticipates claims 8-12 drawn to a method for synthesizing a nucleic acid molecule from a crude preparation containing DNA, said method comprising: a) mixing the crude preparation containing DNA, wherein the DNA functions as a desired nucleic acid template, with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template (claim 8), wherein said peptide or polypeptide having ribonuclease activity is selected from the group consisting of RNase A, RNase T1, RNase H, RNase S, RNase B, RNase C, RNase T2 and enzymatically

active fragments, variants, derivatives or mutants thereof (claim 9), wherein said mixture further comprises one or more components selected from the group consisting of: a) at least one nucleotide; b) at least one suitable buffer for nucleic acid synthesis; and c) at least one primer (claim 10), wherein said DNA polymerase is thermostable (claim 11), and wherein said DNA polymerase is *Taq* DNA polymerase (claim 12).

Applicants traverse this rejection on the basis that the Maudru et al. reference does not teach the claimed methods because Maudru et al. start with a "pure" RNA , and it is unlikely that one of ordinary skill in the art would consider a "purified RNA and its cDNA" as a "crude preparation". As in the previous office actions, this argument is not found persuasive, because as previously stated it is believed that such a preparation of RNA and cDNA would be considered a crude preparation, absent proof otherwise. As discussed above a reasonable interpretation of the terms "crude preparation containing DNA is any preparation of DNA which also includes other cellular macromolecules, i.e. RNAs proteins, lipids, cell debris etc. As the preparation of Maudru et al. following the reverse transcriptase step clearly includes at least DNA, RNA and protein it would be considered a crude preparation. It is acknowledged that Maudru et al. teach a method that begins with a RNA-containing preparation, but this is converted to a DNA-containing preparation during the reverse transcriptase step. It is at this point where Maudru et al. anticipates the claimed methods in that the starting material is now a DNA containing preparation which also contains RNA and proteins and in as much as no additional purification steps have been done to this preparation, it could be considered a "crude DNA-containing preparation". While it is true that the

method of Maudru et al. includes an initial step that converts a "pure" RNA preparation into a "crude" preparation containing DNA, the recited method of applicants claims does not exclude other steps prior to the recited steps.

12. Claims 8-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Don et al. (Nucleic Acids Research 21(3): page 783, 1993).

The rejection was originally stated as it applies to claims 8-12 in an earlier office action.

Don et al. teach a "one tube reaction" for synthesis and amplification of total cDNA from a small number of cells. Specifically, Don et al. teach a method of synthesizing a nucleic acid comprising mixing nucleic acid template, MMLV reverse transcriptase, RNase H, KGB buffer, T4 DNA polymerase and *Taq* DNA polymerase. It is acknowledged that Don et al. teach a method that begins with a RNA-containing preparation, but this is converted to a DNA-containing preparation during the reverse transcriptase step. The method taught by Don et al. comprises adding reverse transcriptase to a RNA preparation which is converted to cDNA, followed by the addition of RNase H and *E. coli* DNA polymerase. It is at this point where Don et al. anticipates the claimed methods in that the starting material is now a DNA containing preparation and in as much as no additional purification steps have been done to this preparation, it could be considered a "crude preparation containing DNA".

Thus Don et al. anticipates claims 8-12 drawn to a method for synthesizing a nucleic acid molecule from a crude preparation containing DNA, said method

comprising: a) mixing the crude preparation containing DNA, wherein the DNA functions as a desired nucleic acid template, with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template (claim 8), wherein said peptide or polypeptide having ribonuclease activity is selected from the group consisting of RNase A, RNase T1, RNase H, RNase S, RNase B, RNase C, RNase T2 and enzymatically active fragments, variants, derivatives or mutants thereof (claim 9), wherein said mixture further comprises one or more components selected from the group consisting of: a) at least one nucleotide; b) at least one suitable buffer for nucleic acid synthesis; and c) at least one primer (claim 10), wherein said DNA polymerase is thermostable (claim 11), and wherein said DNA polymerase is *Taq* DNA polymerase (claim 12).

Applicants traverse this rejection as above rejection by Maudru et al., on the basis that claim 8 has been amended to require a crude preparation containing DNA as the starting sample, and applicants point out that Don et al. require purified RNA as the starting material. This argument is not held persuasive because as discussed above the recitation "crude preparation containing DNA" is encompassed by the preparation used by Don et al. following the reverse transcription step. As discussed above, it is acknowledged that Don et al. teach a method that begins with a RNA-containing preparation, but this is converted to a DNA-containing preparation during the reverse transcriptase step. While applicants argue that a preparation containing purified RNA and its cDNA would not be considered by a skilled artisan to be a "crude preparation"

this is not persuasive, as this preparation contains at the least RNA, DNA, reverse transcriptase, ribonuclease, RNase H and nucleotides and thus a multitude of different compounds which would be considered to be a "crude preparation". It is at this point where Don et al. anticipates the claimed methods in that the starting material is now a DNA containing preparation and in as much as no additional purification steps have been done to this preparation, it could be considered a "crude preparation containing DNA". Thus, Don et al. continues to anticipate the claimed methods of claims 8-12.

13. Claims 57-59 and 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Kenten et al. (U.S. Patent No: 6,048,687, filed 6/7/1995).

Kenten et al. teach a method for synthesizing and detecting a specific nucleic acid comprising adding to a sample containing the specific nucleic acid a primer, a DNA-directed DNA polymerase and a ribonuclease along with other components and incubating the reaction mixture for a sufficient time to amplify/synthesize the nucleic acid sequence. The "nucleic acid" referred to by Kenten et al. refers to a polynucleotide of any length, including DNA or RNA chromosomes or fragments thereof (column 7, lines 12-15), which clearly includes "genomic DNA". It is noted that Kenten et al. teach the addition of a ribonuclease, and this is encompassed by claim 58 drawn to a number of specific ribonucleases, as well as fragments, variants derivatives or mutants thereof. Kenten et al. further teach that the nucleotides may be linked to biotin and digoxigenin, thus encompassing detectably labeled nucleotides as recited in claim 62.

Thus, Kenten et al. anticipates claims 57-59 and 62 drawn to a method for synthesizing a nucleic acid molecule, said method comprising: a) mixing a nucleic acid template, wherein said nucleic acid template is genomic DNA, with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template (claim 57), wherein said peptide or polypeptide having ribonuclease activity is selected from the group consisting of RNase A, RNase T1, RNase H, RNase S, RNase B, RNase C, RNase T2 and enzymatically active fragments, variants, derivatives or mutants thereof (claim 58), wherein said mixture further comprises one or more components selected from the group consisting of: a) at least one nucleotide; b) at least one suitable buffer for nucleic acid synthesis; and c) at least one primer (claim 59), wherein one or more of said nucleotides are detectably labeled (claim 62).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maudru et al. or Don et al.

This rejection was originally made over claims 8-13. Claims 8-12 are included in this 103 rejection to the extent that they clearly encompass methods with the limitation of claim 13 wherein said nucleotides are detectably labeled. This particular embodiment of claims 8-12 are not anticipated although as discussed above, claims 8-12 also embrace embodiments which are anticipated. Thus both the 102 and 103 rejections are proper.

As discussed above, Maudru et al. examine the cause of and teach a method for the elimination of background signals in a modified polymerase chain reaction-based reverse transcriptase assay and Don et al. teach a "one tube reaction" for synthesis and amplification of total cDNA from a small number of cells. Neither reference teaches the inclusion of a detectably labeled nucleotide in the taught methods.

One of ordinary skill in the art at the time of filing would have been motivated to use a detectably labeled nucleotide in the methods of synthesizing a nucleic acid molecule as taught by both Maudru et al. and Don et al. (See above 102 rejections based on each of these references) so that the synthesized DNA molecule could be used as a nucleic acid probe to identify related DNA molecules from other organisms, or other DNA libraries, or so that the label could be used as a means of measuring the amount of nucleic acid synthesized. One would have had a reasonable expectation of success based on the high level of knowledge in the art of using

radioactive nucleotides in DNA synthesis reactions to detectably label the synthesized product.

Applicants traverse this rejection as the above 102 rejection on the basis that the method of Maudru et al. does not teach a method which begins with a "crude preparation containing DNA" and there is no motivation to modify the teaching of Maudru et al. because applicants submit that Maudru et al. stress the importance of purified RNA and applicants submit a recitation from Maudru et al. supporting this point. Applicant is reminded as discussed above under the 102 rejection, that the method which is rejected by Maudru et al. begins after the "purified RNA" has been used as a template for the synthesis of the first cDNA strand, and it is at this point that the preparation is a crude preparation containing DNA and it is at this point that the addition of ribonuclease is desirable. At this point in the taught method, the RNA material is no longer necessary or desired. This argument supported by the fact that it is at this point that Maudru et al. employ the activity of the added ribonuclease, as discussed above in the 102 rejection. Argument that the inclusion of RNase in the reaction is not obvious as applicants appear to state are not understood because the method of Maudru et al. and Don et al. unquestionably include RNase and this limitation is expressly anticipated. It is only the limitation that the nucleotides used in the method be detectably labeled that is not expressly anticipated and it is this difference that the examiner maintains would have been obvious to the ordinary skilled artisan.

Applicants argument with respect to rejected claim 13 is based on the above reasons that claim 8 is not made obvious, this argument not found persuasive as discussed above.

Applicants traverse the above rejection based on Don et al. on the same basis as the traversal based on Maudru et al. and this is not found persuasive for the same reasons discussed above in response to the rejection based on Maudru et al. As in the above discussion of Maudru et al., it is acknowledged that Don et al. makes no mention of detectably labeled nucleotides, but as discussed above this limitation would have been obvious for the reasons stated above.

15. Claims 8-13 and 57-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schowalter et al. (Analytical Biochemistry, Vol 177, 1989, pages 90-94), Maudru et al. (Journal of Virological Methods 66: 247-261, July 1997) and Sambrook et al. (Molecular Cloning A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory Press, 1989, pages 1.33-1.52.).

Schowalter et al. teach the generation/synthesis of radiolabeled DNA and RNA probes with thermostable *Taq* DNA Polymerase using the polymerase chain reaction. Specifically Showalter et al. teach the synthesis of nucleic acid molecules comprising the mixing of the nucleic acid template with thermostable *Taq* DNA polymerase, specific primers, nucleotides including a radioactively labeled nucleotide and incubating the above reaction mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said nucleic acid template. Showalter et al. further

teach the application of these methods to the synthesis of labeled nucleic acids generated from plasmid (vector) inserts and the use of these methods for the generation of labeled probes directly from genomic DNA or DNA inserted into a cloning vector such as M13. In the application of these methods to the synthesis of labeled nucleic acids generated from plasmid (vector) inserts, Showalter et al. teach that these methods obviate the need for CsCl gradient purification of the DNA template or other large scale methods of prior DNA preparation, thus they include synthesis from "crude preparations containing DNA" , although they acknowledge that high background with spurious bands will result from the presence of contaminating sequences. Schowalter et al. do not teach the use of a polypeptide having ribonuclease activity in the disclosed methods.

As discussed above under the 102 rejection, Maudru et al. teach that the background signal of the PCR-based reverse transcriptase (PBRT) assay is due to an intrinsic RNA-dependent DNA polymerase activity of the *Taq* DNA polymerase enzyme and they teach that this background signal could be eliminated by the addition of a ribonuclease to the amplification reaction.

Sambrook et al. teach that cesium chloride gradients are used to remove contaminating RNA, and protein from plasmid DNA preparations.

One of ordinary skill in the art at the time of filing would have been motivated to add a polypeptide with ribonuclease activity to the methods taught by Schowalter et al. in order to remove residual RNA sequence contamination from the targeted nucleic acid template in any preparation which would contain substantial amounts of RNA in order to decrease the level of background signal from the synthesized radiolabeled nucleic acid

probes. As the ordinary artisan would know that any nucleic acid preparation that has not been purified, such as genomic DNA or plasmid DNA contains substantial amounts of contaminating RNA. The motivation for the removal of these contaminating sequences is so that nucleic acid probes can be synthesized that are more specific for the desired target nucleic acid sequence. This is supported by both Schowalter et al. who teach that if the generated probes are contaminated, high background and spurious bands will result, and Maudru et al. who teach that the background signals of PCR based nucleic acid synthesis reactions is due to an intrinsic RNA-dependent DNA polymerase activity of *Taq* DNA polymerase. The reasonable expectation of success for the inclusion of ribonuclease in the nucleic acid synthesis reaction of Schowalter et al. comes from the high degree of knowledge in the field of nucleic acid synthesis and the results of Maudru et al. who teach that the simultaneous addition of ribonuclease in order to eliminate background signals in the polymerase chain reaction mix containing *Taq* DNA polymerase did not adversely affect the synthesis of the desired nucleic acid products by PCR.

Thus, claims 8-13 and 57-69 drawn to a method for synthesizing a nucleic acid molecule, said method comprising: a) mixing a nucleic acid template, wherein said nucleic acid template is genomic DNA, a DNA contained in a phage DNA cloning vector, or said nucleic acid template is from a crude preparation containing DNA, with one or more thermostable *Taq* DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template

(claims 8, 11, 12, 57, 60, 61, 63, 64, 67 and 68), wherein said peptide or polypeptide having ribonuclease activity is selected from the group consisting of RNase A, RNase T1, RNase H, RNase S, RNase B, RNase C, RNase T2 and enzymatically active fragments, variants, derivatives or mutants thereof (claims 9, 58 and 65), wherein said mixture further comprises one or more components selected from the group consisting of: a) at least one nucleotide; b) at least one suitable buffer for nucleic acid synthesis; and c) at least one primer (claims 10, 59 and 66), and wherein one or more of said nucleotides are detectably labeled (claims 13, 62 and 69) are made obvious by Schowalter et al., Maudru et al. and Sambrook et al.

Claims 8-13 are included in this rejection, as the claimed methods would be obvious even if one accepted applicants above argument that Maudru et al. does not anticipate a "crude preparation containing DNA".

Remarks

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
March 11, 2002